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(71)(72) Applicant and Inventor: CHASIN, Mark [US/US]; 3 Wayne Court, Englishtown, NJ 07726 (US).

(74) Agent: BRENEMAN, William, D.; Breneman & Georges, Suite 290, International Square, 1850 K Street, N.W., Washington, DC 20006 (US).

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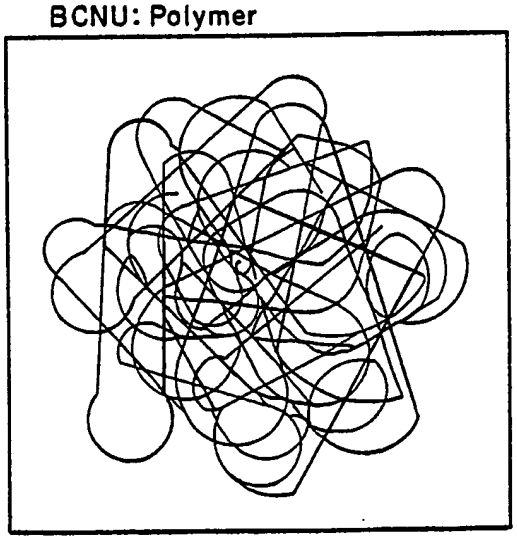

(57) Abstract

A bioerodible controlled drug release implant is produced which contains a suitable pharmaceutically active compound dispersed uniformly throughout a polymeric matrix. An implant is prepared by dissolving a suitable bioerodible polymer in an organic solvent followed by the addition of a predetermined amount of a pharmaceutical preparation. The solution is mixed until the polymer and drug are fully dissolved. The solution is then evaporated to dryness where the dry polymer/drug composition is reduced to a granular composition which is then formed by compression molding into the desired shaped. The pharmaceutical preparation may be a drug in pure form or a solution of a drug dissolved in a suitable solvent. In the event the solution of the drug is immiscible with the polymer solution a suitable dispersing agent is included in the drug solution to disperse the drug with the polymer. Devices formed by the method are suitable for controlled drug release devices, bone or other prosthesis and the like.

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METHOD OF FORMING BIOERODIBLE IMPLANTS FOR IMPROVED CONTROLLED DRUG RELEASE

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a method of producing bioerodible implants and the resultant bioerodible implant having a medicament uniformly dispersed throughout a polymeric matrix. More particularly the invention is directed to sustained drug release polymeric implants which approach zero order release.

Description of the Prior Art

In conventional drug delivery systems it is difficult to dispense a drug at a rate which will continuously maintain the most effective drug concentration in the patient throughout the period of time treatment is needed. One approach to effectively maintain a constant rate of release of a drug is through the use of bioerodible implants formed from a bioerodible polymer and an effective amount of a drug. With the development of polymers which erode in vivo at a constant rate into nontoxic components has come an increase in the interest of bioerodible controlled drug release implants.

Bioerodible polymeric controlled drug release systems have the major advantage of not requiring removal of the device after depletion of the drug since the polymers degrade completely into nontoxic components. Further

advantages include the ability to surgically implant the device at a preselected site to deliver the drug only to that desired site and at the desired concentration. An implantable controlled drug release device formed from a bioerodible polymer is able to release a drug to a selected site at concentrations much higher than could ever be achieved by conventional intraveneous or intramuscular administration. By selecting a polymer with desired release and erosion rates and incorporating a desired amount of a drug the drug concentration at an implant site can be thousands of times higher than elsewhere in the body often without the detrimental effects to other parts of the body caused by the drug at the higher dosage rates. In contrast it is not possible to achieve a continuous high drug concentration at one site when the drug is introduced systemically without raising the concentration throughout the body. The ideal implantable controlled drug release device is formed from a polymer which exhibits a constant erosion rate over time and is able to release the drug at a constant rate. True zero order release is the linear release of a drug in relation to the rate of erosion of the polymeric matrix.

The rate of surface erosion of the polymer is the primary factor in controlling the rate of release of the drug. When the surface erosion of the polymeric device is constant the rate of release of the drug in a homogeneous mixture should be proportional to the surface area of the system. The optimum controlled release device erodes at a

constant preselected rate with only minimal diffusion from the inner body of the polymer matrix.

Although several types of controlled release devices have been developed the type which has proven most effective are the devices where the drug is dispersed throughout the polymer in a homogeneous matrix. The homogeneous matrix has heretofore been sought in the prior art by a mechanical mixing followed by either compression molding, injection molding or solvent casting.

In addition to forming a homogeneous mixture of a drug and polymer a bioedible implant in order to be commercially feasible must be produced at a high rate with minimal variations between the implants. One of the more common methods of producing the polymeric implants simply mechanically mixes to randomly disperse the powdered drug in the proper proportion with the polymer. A predetermined amount of the mixture is then pressed into a tablet, wafer or other suitable shape.

This prior art method of preparing bioerodible controlled release implants, although simple and efficient, does not produce a device which erodes at a constant rate or displays a true zero order release of the drug. In vivo and in vitro tests conducted using these devices display a fluctuating rate of release of the drug and accordingly a fluctuation in the concentrations of the drug within the surrounding environment.

The fluctuating release rate of the prior art

compression molded implants is believed to be due primarily to the relatively large particles of the drug imbedded in or surrounded by the polymeric matrix. As such, there tends to be distinct particles of the drug of different sizes randomly dispersed throughout the matrix.

When the powdered composition is formed by simply mixing a powdered drug with a powdered polymer and compressing the mixture, the resulting implant does not show a completely uniform distribution of the drug throughout the polymer matrix. When the polymer is implanted in tissue the outer surface of the polymer erodes to expose these randomly dispersed particles which then dissolve in the surrounding fluid environment. Since the drug particles are not uniformly but rather randomly dispersed throughout the polymer there are times when no drug particles are exposed to be released and other times when undesirably large numbers of the drug particles are exposed and are released. The result is that as the polymer erodes the rate of release of the drug is uncontrolled and continuously rises and falls. This prior art process of manufacturing bioerodible drug release implants accordingly does not produce a satisfactory implant which exhibits or more closely approaches zero order release of the drug.

Another prior art method of manufacturing bioerodible drug release implants is by injection molding. Injection molding processes involve essentially heating the polymer to the glass transition point or melting point and injecting the fluid polymer and drug into a suitable mold.

The drug can be mixed in powder form with the polymer prior to melting or it can be added as a dispersion or suspension to the melted polymer.

Injection molding does not produce a suitable implant which sufficiently exhibits or approaches zero order release. The melt dispersion of polymer and drug as with the mixing of the powders does not produce a sufficiently uniform distribution of the drug throughout the polymer matrix to enable a constant rate of release. Although some of the drug may be dissolved in the melted polymer a large number of drug particles remain undissolved which when exposed upon erosion of the surrounding polymer cause a sudden release of an undesirably large amount of the drug to the surrounding tissue or fluid.

Further disadvantages of the melting step result when the heat required to reach the melting point of the polymer causes the drug or the polymer to degrade. At these higher temperatures the probability of drug to polymer interaction is much greater which further reduces the effectiveness of the bioerodible implant.

Another prior art method commonly employed in producing bioerodible devices is by solvent casting techniques. This technique involves essentially dissolving the polymer in a suitable solvent, such as methylene chloride, followed by the addition of a drug in the desired proportions. Once the polymer and drug are dissolved in the solvent the solution is poured onto a flat surface where the

solvent is evaporated to form a thin film of the polymer drug matrix.

Solvent casting generally results in a distribution of the polymer and drug which is more uniform than compression molding or injection molding technigues and has the advantage over injection molding of avoiding the possibility of degradation of the drug or polymer. Solvent casting is suitable, however, only for making thin flexible films and is generally not used for larger implants or prosthesis where thicker or larger devices are required. Since the solvent casting technique is limited to the formation of thin films which must be cut into a desired shape to obtain a suitable implant high volume production is not cost effective and the size and shape of the implant is unduly restricted. In addition the cutting of an implantable device from a thin film or sheet inherently results in some waste and scrap which must be redissolved and recast to make the process economically feasible. Since solvent casting is only suitable for thin films the resulting implant will generally be rather small and as such capable of releasing a rather small amount of a drug for only a limited time.

Presently the only economically feasible method for manufacturing bioerodible and other polymer/drug matrices is by compression molding of powders since this is the only procedure which can be carried out at high volume rates. Moreover, compression molding can be used for forming implants of any desired shape or size. As discussed above, however, compression molding procedures have the distinct

disadvantage in failing produce a bioerodible controlled drug release implant which can optimally exhibit or approach zero order release.

There is accordingly a need for a bioerodible controlled drug release device which exhibits zero order release of the drug over time, demonstrates uniform drug distribution, can be compounded without degrading or causing drug and polymer interaction and which can be manufactured in large quantities efficiently and economically. The present invention accordingly relates to a bioerodible device which is able to deliver a drug at a predetermined continuous rate for extended periods of time. Moreover, the invention is directed to a method of preparing bioerodible implants in any desired shape without degradation to the drug and polymer and which is cost effective and capable of producing large quantities of the devices in rapid succession.

SUMMARY OF THE INVENTION

The disadvantages and limitations of the prior art bioerodible implants and the methods of preparation are obviated while providing an efficient bioerodible implant and method of preparation which exhibit a release rate which more closely approaches a zero order release than the prior art methods.

The present invention relates primarily to a method of manufacturing bioerodible implants in a manner in which the drug is dispersed evenly and uniformly throughout the polymeric matrix. In the preferred form of the invention the

polymer is first dissolved in a suitable solvent. The desired drug is then added to the polymer solution in the desired proportion and mixed until completely dissolved. When the polymer and the drug are both dissolved the solution is either spray dried to a powder or poured into a suitable vessel where the solvent is removed, preferrably by evaporation under vacuum. Once dried the polymer-drug matix is ground to a powder where it can be formed by compression molding into the desired shape and size.

The resulting implantable article possesses superior release rates over extended periods of time compared to the prior art devices since the drug is evenly dispersed throughout the polymer matrix. By dissolving the drug in solution with the dissolved polymer the drug tends to be dissolved in the polymer and dispersed throughout the polymer matrix on a molecular level as the solvent is removed.

The polymer/drug matrix in a powder form can be used to produce implantable articles of any desired shape using standard compression molding techniques. The molded articles formed from discrete particles display a uniform distribution of the drug throughout the article resulting in an implantable bioerodible article which releases the drugs to the surroundings at a constant and uniform rate.

BRIEF DESCRIPTION OF THE DRAWINGS

Other advantages of the invention will become apparent to those skilled in the art from the following detailed description of the invention in conjunction with the

accompanying drawings in which:

FIGURE 1 is a representation of the drug distribution in a prior art controlled drug release device.

FIGURE 2 is a representation of the drug distribution in a controlled drug release device formed according to the present invention.

FIGURE 3 is a graph of samples showing the distribution of BCNU throughout the polymer matrix produced according to the present invention.

FIGURE 4 is a graph of samples showing the distribution of BCNU throughout the polymer matrix produced according the prior art method.

FIGURE 5 is Differential Scanning Calorimetry curve for pure BCNU.

FIGURE 6 is a Differential Scanning Calorimetry curve for pure PCPP:SA (20:80).

FIGURE 7 is a Differential Scanning Calorimetry curve for a BCNU/PCPP:SA powdered mixture prepared by the prior art methods.

FIGURE 8 is a Differential Scanning Calorimetry curve for a BCNU/PCPP:SA matrix prepared according to the present invention.

FIGURE 9 is a Differential Scanning Calorimetry curve for Examples VI-IX of a BCNU/PCPP:SA matrix prepared according to the present invention.

FIGURE 10 is a Differential Scanning Calorimetry curve for Examples X-XIII of BCNU/PCPP:SA prepared according

to the prior art.

FIGURE 11 is a comparison graph plotting the % of BCNU released over time for wafers containing 2.5% BCNU formed according to the prior art and the novel methods.

FIGURE 12 is a comparison graph plotting the % BCNU released over time from wafers containing 10% by weight BCNU according to the prior art and the novel method.

DESCRIPTION OF THE PREFERRED EMBODIMENT

A drug containing bioerodible polymeric matrix having a uniform composition throughout the implant has been developed which can be formed by compression molding techniques into implantable articles which approach a zero order release rate of the drug over an extended period of time.

The polymer employed can be any suitable polymer which degrades in vivo into non-toxic components and degrades at a steady rate from the outermost surface inwardly. The ideal polymers are those which undergo surface erosion with a steady state of hydrolytic degradation at the surface at a faster rate than the rate of water penetration onto the bulk of the matrix.

The ideal polymers for bioerodible articles generally have a hydrophilic backbone with water labile linkages. Polymers which have been studied with varying success for bioerodible controlled delivery articles include polyesters, polyorthoesters, polyamides, polyurethanes, polyacrylonitriles and polyphosphazenes. Presently the most

promising bioerodible polymers appear to be the polyanhydrides and particularly the high molecular weight polyanhydrides as described in Rosen, et al Biomater. Vol 4, April 1983, and Leong, et al Journal of Biomedical Materials Research 20,51 (1986).

Polyanhydrides which have been shown to demonstrate superior bioerodible qualities include, polysebacic acid, 1,3-bis (p-carboxyphenoxy) propane, polyterephthalate and polymers from other aliphatic and aromatic dicarboxylic acids and copolymers of these acids. The rates of the erosion and rate of release of the drug can be controlled or altered by the specific polymer. By controlling the ratio of aliphatic and aromatic nonomers and the molecular weight of the polymer as is known in the prior art the erosion rates and uniformity of erosion can be controlled as desired depending on the intended location of the device and the type of treatment needed.

The method according to the present invention includes the steps of dissolving the polymer in a suitable solvent while stirring continuously. The preferred solvent is methylene chloride although any nonreactive solvent can be used. Examples of suitable solvents include but are not limited to carbontetrachloride, tetrahydrofuran and ethylacetate. It is of course essential that the polymer is not reactive with the solvent and that the particular drug selected is soluble or miscible in the resulting polyanhydride and solvent solution.

When the polymer is completely dissolved a

predetermined quantity of a drug is added to the polymer solution and stirred until completely dissolved. In the preferred embodiment of the invention the solution is spray dried using conventional techniques. This method generally sprays the drug polymer solution into a heated chamber maintained at reduced pressure to remove the solvent. The resulting product is a fine powder or granular composition which does not require further processing.

Alternatively the drug:polymer solution may be transferred to a suitable evaporation vessel such as a roto-evaporatior where a vacuum is applied to remove the solvent. This drying method is, however, more time consumming and requires a further grinding step to reduce the dried material to a powder.

Regardless of the method employed the powdered drug polymer composition can be stored or transferred to a suitable molding apparatus. The powdered drug polymer composition is particularly useful for compression molding techniques where the powder can be formed at a commercially acceptable rate into any desired shape or size. Alternatively, if desired the drug polymer composition can be redissolved in a suitable solvent and cast using standard solvent casting or film forming procedures.

Any number of suitable solvents which are easily removed from the solution and nonreactive with the drug or polymer can be employed in practicing the present invention.

In the preferred embodiment the solvent is selected where both the desired polymer and the drug are readily soluble. In this manner the polymer can be first dissolved in the solvent followed by the addition of the pure drug. Depending on the characteristics of the drug employed the drug can alternatively be added in the form of a suitable pharmaceutical preparation formed by dissolving a predetermined amount of the drug in the solvent.

It is further possible to dissolve the drug and the polymer in different solvents and then combine the two solutions. When the two different solvents are miscible the two solutions can simply be mixed together. In the event the two different solvents are immiscible a suitable surfactant or dispersing agent can be employed to form a dispersion of the drug and polymer. The resulting solution or dispersion is then dried by spray drying or evaporation procedures as described above.

The bioerodible drug release implants produced according to the present invention have been found useful for treating a variety of disorders. Examples of the types of drugs which can be employed in the implant include anticonvulsants, antiepileptics, anticancer, anti-parkinsonism agents, antihypertensives, antibacterials, antiviral, antifungal, narcotic antagonists, vascular agents, stimulants, agents for treating Alzheimer's disease and phamaceuticals used to treat other disorders of the central nervous system.

The uniform release rates of bioerodible drug

release implants when prepared according to the present invention are due in part to the uniform distribution of the drug throughout the polymeric matrix. The prior art method of mechanically mixing the powdered polymer with the powdered drugs results in a random distribution of drug particles throughout the matrix as represented in Fig. 1. This arrangement results in random exposure of the drug particles as the polymer erodes causing a fluctuation in the release rate of the drug.

Conversely the method of forming bioerodible implants according to the present invention results in a uniform distribution of the drug with the polymer matrix. This uniform distribution is due in part to the drug actually being dissolved in the polymer as represented generally in Fig. 2.

The superior rate of drug release and uniform dispersion of the drug within the polymer matrix is further demonstrated in the following non-limiting examples.

EXAMPLE I

Anhydrous methylene chloride was selected as the preferred solvent since it is readily available, inexpensive and is a good solvent for many polymers and drug compounds. To 168 ml of methylene chloride was added 5.4 grams of a 20:80 poly 1,3-bis (p-carboxyphenoxy) propane:sebacic acid copolymer (PCPP:SA) prepared according to known polymerization procedures. The mixture was then stirred continuously at room temperature until the PCPP:SA was

completely dissolved.

Once the PCPP:SA polymer was dissolved 0.6 grams of BCNU (1,3-bis (2 chloroethyl) 1-nitrosourea) was added slowly to the solution with continued stirring until completely dissolved. The PCPP:SA/BCNU solution was spray dried by spraying into a closed heated chamber maintained under dry nitrogen. The spray drying proceedure is found effective to remove all traces of the methylene chloride leaving behind a powdered drug:polymer matrix. A portion of the dry powder weighing 0.2 grams was transferred to a mold and pressed into a wafer-like form having dimensions of 1 mm thick by 1.4 cm in diameter suitable for implanting in vivo in a patient. When prepared according to the novel method the implantable bioerodible controlled release device has a far more uniform distribution of the BCNU within the polymer matrix than compared with the prior art method of forming implantable articles.

The wafer formed according to the above procedure was divided into 10 portions. Each portion was redissolved in methylene chloride and subjected to HPLC (high pressure liquid chromatography) to determine the BCNU content of each portion. The results of this analysis as shown in the graph of Fig. 3 demonstrate that each portion of the wafer contained an average of 10.40% BCNU by weight of the polymer (PCPP:SA) with a standard deviation of only 0.17. This results in a percent standard deviation (i.e. the standard deviation (0.17) divided by the mean value (10.40)) of only a 1.6% variation between the tested portions of the wafer.

EXAMPLE II

For purposes of comparison, the prior art method of forming implantable articles was carried out by mechanically mixing 0.18 grams of dry powdered PCPP:SA polymer with 0.02 grams of BCNU. The mixture of dry powdered polymer and powdered BCNU was transferred to a similar mold and compressed into a wafer suitable for in vivo implantation. The device formed by this prior art method contained a theoretical average of 10% BCNU by weight.

The prior art wafer was divided into 10 portions in the manner as described above and each portion was subjected to HPLC to determine the BCNU content of each portion revealing an average of 9.82% BCNU by weight for each portion. The distribution between the portions is shown in Fig. 4 exhibiting a standard deviation of 1.14. The percent standard deviation of this prior art method showed a variation of 11.6% between the segmented portions.

As can be seen by the comparison of the novel method in Fig. 3 (Example I) and the prior art method in Fig. 4 the wafer produced according to the invention demonstrates a 10-fold improvement in uniformity of BCNU throughout the polymeric matrix.

EXAMPLE III

The additional improved and unique characteristics of the novel method of forming bioerodible implantable devices compaired to the prior art methods was determined using Differential Scanning Calorimetry (DSC) analysis. This

type of analysis offers data demonstrating the melting point of discrete paricles as represented by distinct peaks for each melting point.

Referring to Fig. 5 the DSC curve is shown for pure BCNU which shows a sharp melting point between 30 and 32 degrees C. Fig. 6 shows a similar DSC curve for the pure PCPP:SA (20:80) polyanhydride copolymer having a broad band between 32 and 60 degrees C. This broad range represents the glass transition range of PCPP:SA (20:80) while the sharper peak represents the melting point between 60 and 65 degrees C.

EXAMPLE IV

The DSC of a PCPP:SA/BCNU wafer produced according to the prior art method of Example II by mechanically mixing dry powders is shown in Fig. 7. The prior art method of preparing wafers for implantation shows two distinct peaks for the melting point of BCNU and the polymer in an essentially additive manner. The existence of the two peaks demonstrates the presence of discrete particles of the drug surrounded by the polymer. It is important to recognize that since the content uniformity of the prior art wafers are so poor the relative heights of the peaks of the BCNU and the polymer melting points will differ from sample to sample.

EXAMPLE V

Referring to Fig. 8 the wafer of BCNU and PCPP:SA prepared according to the novel method of Example I displays unique and unexpected results. The DSC curve does not show distinct melting points for the drug and polymer as with the

prior art article. There is no melting point peak for the BCNU but rather a shift in the melting point of the PCPP:SA and a substantial broadening of the peak. The melting point peak of the novel polymer/drug matrix is shifted slightly lower than the polyanhydride peak of the prior art article.

The above data demonstrate that substantial differences exist between the novel polymer/drug matrix and the prior art. The DSC data shows that the BCNU is actually dissolved in the PCPP:SA which causes the shift in the melting point peak. The absence of a peak at the melting point of BCNU demonstrates that essentially no distinct particles of BCNU remain undissolved in the polymeric matrix. Since the drug is dissolved or at least partially dissolved in the polymer a more uniform distribution of the drug occurs.

To ensure the BCNU did not react with the PCPP:SA four samples of the wafer produced according to the novel method of Example I invention were redissolved in methylene chloride. The solution was then analyzed and assayed for BCNU content using HPLC analysis. This testing consistently recovered essentially all of the BCNU which was unaffected by the process.

EXAMPLES VI-IX

The uniformity of the distribution of the BCNU in the PCPP:SA polymer is further demonstrated by DSC analysis. As can be seen in Fig. 9 four segments identified as Examples VI-IX of a wafer prepared by the prior art method of Example

II were subjected to DSC analysis. The curves of each sample demonstrate a significant variation in BCNU content between the samples as indicated by the different heights of the peaks.

EXAMPLES X-XIII

Referring to Fig. 10 a wafer formed by the process according to Example I when segmented into four parts identified as Examples X-XIII demonstrated a consistent peak with essentially no variation. This data further supports the previous findings of a uniform distribution of BCNU within the polymeric matrix.

EXAMPLE XIV

The release characteristics of the novel bioerodible implant were determined *in vitro*. A first comparison using samples having 2.5% by weight BCNU to PCPP:SA prepared by the novel method of Example I and the prior art method of Example II was conducted as shown in Fig. 11. As can be seen the novel process produces a bioerodible controlled release device which approaches a zero order release of the drug over time as indicated by the more gradual slope of the curve.

EXAMPLE XV

A second sample was prepared which included 10% BCNU by weight of the PCPP:SA polymer using the prior art method of Example II and the method according to the invention of Example I. As shown in Fig. 12 the *in vitro* release rate of the novel controlled drug release device also approaches zero order release when compared to the prior art

as indicated by the more gradual slope of the curve.

The above data further demonstrates that the release characteristics of the controlled release devices are essentially identical and independent of the concentration of BCNU in the polymeric matrix.

Although the above examples were carried out using PCPP:SA and BCNU any combination of polymers and drugs can be implemented using the teachings of the invention to achieve superior drug release rates. The choice of the polymer which can be used is not limited to polyanhydrides as any suitable bioerodible polymeric material can be used. The selection of the appropriate polymer is made by one skilled in the art according to the intended use. Factors which determine the selection of the polymer include the type of drug to be released, the location of the implant and desired duration and rate of release.

The solvent can be selected from any nonreactive solvent although methylene chloride is the preferred solvent. The solvent is selected to ensure the particular polymer and the drug are soluble therein. In the case of the drug being in liquid form the drug should be readily miscible in the solvent with no phase separation. Moreover, the drug must not react with the solvent or the polymer once in solution.

The method according to the present invention enables a relatively shelf stable powder of the polymer and drug to be prepared in larger quantities and which can be readily formed by standard compression molding techniques

into any desired shape and size of implantable article. More importantly the method of the present invention can be used to prepare bioerodible controlled drug release devices which demonstrate superior rates of release of the drug. Although the above example discloses a drug release implant one skilled in the art will easily recognize the method is suitable for molding any device including bone prostheses intended to be surgically implanted in the patient.

The detailed description of the invention is provided for purposes of illustrating the preferred embodiment of the invention. It will be recognized by those skilled in the art that the preferred embodiment is not intended to be limited to the disclosed embodiment as they may be readily modified by those skilled in the art. It is readily apparent that other modifications not mentioned herein can be made by those skilled in the art without departing from the spirit and scope of the invention as claimed in the following claims.

WHAT IS CLAIMED IS:

1. A method of preparing a polymeric matrix of a solid polymer having a pharmaceutical preparation uniformly dispersed therein comprising the steps of;

a) dissolving at least one polymeric compound in a first solvent to form a polymer solution;

b) dissolving at least one pharmaceutical preparation in said polymer solution;

c) reducing said polymer solution to a granular composition of said polymeric compound and said pharmaceutical preparation and;

e) molding said granular composition into a solid polymeric matrix.

2. The method according to claim 1 wherein said pharmaceutical preparation comprises a drug which is soluble in said first solvent.

3. The method according to claim 1 wherein said pharmaceutical preparation comprises a solution of a drug dissolved in an amount of said first solvent.

4. The method according to claim 1 wherein said pharmaceutical preparation comprises a drug which is miscible in said first solvent.

5. The method according to claim 1 wherein said pharmaceutical preparation comprises a solution of a drug dissolved in a second solvent, wherein said second solvent is miscible with said first solvent.

6. The method according to claim 5 wherein said pharmaceutical preparation further comprises a dispersing agent dissolved in a second solvent.

7. The method according to claim 2 wherein said drug is 1,3 bis (2 chloroethyl) 1-nitrosourea.

8. The method according to claim 1 wherein said polymeric compound is a biocompatible bioerodible polymer.

9. The method according to claim 8 wherein said polymeric compound is selected from the group consisting of polyanhydrides, polyesters, polyorthoesters, polyamides, polyurethanes, polyacrylonitriles and polyphosphazenes.

10. The method according to claim 9 wherein said polymeric compound is a copolymer.

11. The method according to claim 9 wherein said polymeric compound is 1,3-bis (p-carboxyphenoxy) propane sebacic acid copolyanhydride.

12. The method according to claim 1 wherein said first

solvent is selected from the group comprising methylene chloride, carbontetrachloride, tetrahydrofuran and ethylacetate.

13. The method according to claim 1 wherein said step of reducing said polymer solution to a granular composition is by evaporation of said solvent under vacuum to form a solid and grinding said solid to a granular form.

14. The method according to claim 1 wherein said step of reducing said polymer solution to a granular composition is by spray drying.

15. The method of claim 1 wherein said granular composition is compressed to form an implantable bioerodible controlled drug release article.

16. The method according to claim 15 wherein said controlled drug release implantable article exhibits a drug release rate approaching zero order.

17. The method according to claim 1 wherein said polymeric matrix is a prosthesis.

18. The method according to claim 1 wherein said prosthesis is a bone prosthesis.

19. The method according to claim 1 wherein said pharmaceutical preparation is disssolved in said polymeric compound.

20. A method of forming a bioerodible controlled drug release implantable device having a uniform distribution of a pharmaceutical throughout a polymeric matrix, said method including the steps of:

a) dissolving at least one biocompatible, bioerodible polymer in a solvent to form a polymer solution;

b) dissolving an effective amount of at least one pharmaceutical preparation in said polymer solution;

c) removing said solvent from said polymer solution containing said pharmaceutical preparation to form a granular composition; and

d) forming said granular composition polymeric matrix into a bioerodible controlled drug release implantable device.

21. The method according to claim 20 wherein said solvent is removed by spray drying said polymer solution.

22. The method according to claim 20 wherein said pharmaceutical preparation comprises a bioactive compound.

23. The method according to claim 20 wherein said

pharmaceutical preparation comprises a solution of a drug in an amount of said solvent.

24. The method according to claim 20 wherein said polymer is a polyanhydride.

25. The method of claim 24 wherein said drug is 1,3 bis (2 chloroethyl) 1-nitrosourea.

26. The method according to claim 20 wherein said solvent is an organic solvent.

27. The method according to claim 26 wherein said solvent is methylene chloride.

28. The method according to claim 20 wherein said solvent is removed by evaporation under vacuum.

29. The method according to claim 20 wherein said granular composition is compression molded into said bioerodible controlled drug release implantable device.

30. The method according to claim 29 wherein said controlled drug release implantable device exhibits a drug release rate approaching zero order.

31. The method according to claim 20 wherein said

pharmaceutical preparation is soluble in said polymer.

32. The method according to claim 20 wherein said polymer is 1,3-bis-(p-carboxyphenoxy) propane sebacic acid copolymer.

33. A method of forming a bioerodible controlled drug release implant having a uniform distribution of a pharmaceutical, said method comprising the steps of:

a) dissolving at least one biocompatible, bioerodible polymer in a first solvent to form a polymer solution;

b) combining an effective amount of a pharmaceutical preparation to said polymer solution, said pharmaceutical preparation comprising a solution of at least one pharmaceutical and a dispersing agent in a second solvent wherein said second solvent is immiscible in said first solvent;

c) removing said first and second solvents from said polymer solution to form a granular composition; and

d) forming said granular composition into a controlled drug release implant.

34. The method of claim 33 wherein said controlled drug release implant is formed by compression molding said granular composition.

35. The method of claim 33 wherein said first and second solvents are removed by spray drying said polymer solution.

36. The method of claim 33 wherein said pharmaceutical is a central nervous system affecting drug.

37. A bioerodible controlled drug delivery article comprising a drug uniformly dispersed in a polymeric matrix produced by a method including the steps of;

a) dissolving a biocompatible, bioerodible polymer in a solvent;

b) dissolving at least one bioactive drug in said solvent to form a solution;

c) removing said solvent from said solution to form a granular polymer matrix; and

d) forming said granular polymer matrix into an implantable bioerodible controlled drug release article.

38. The article according to claim 37 wherein said drug is dissolved in the polymer.

39. The article according to claim 37 wherein said bioerodible article exhibits near zero order release of said drug when implanted in vivo.

40. The bioerodible controlled drug delivery article according to claim 37 wherein said polymer is a polyanhydride.

41. The bioerodible controlled drug delivery article according to claim 40 wherein said polyanhydride is a 1,3 bis (p-carboxyphenoxy) propane sebacic acid copolymer.

42. The bioerodible controlled drug delivery article according to claim 40 wherein said solvent is removed by evaporation under vacuum.

43. The bioerodible controlled drug delivery article according to claim 40 formed by compressing said granular polymer matrix into a solid polymeric matrix.

Fig. 1

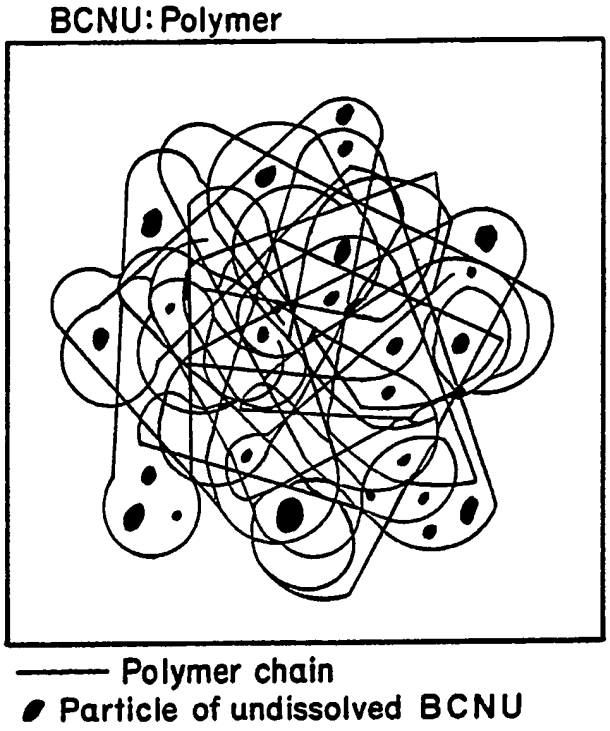

BCNU: Polymer
Polymer chain
Particle of undissolved BCNU

Fig. 2

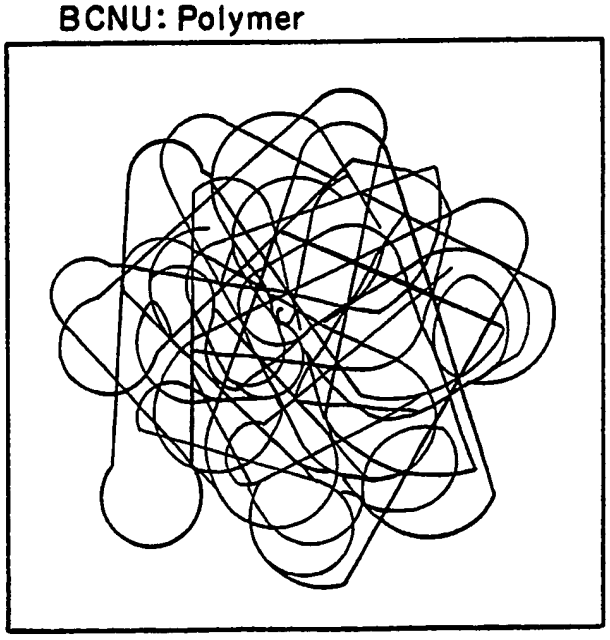

BCNU: Polymer
Polymer chain containing dissolved BCNU

Fig.3

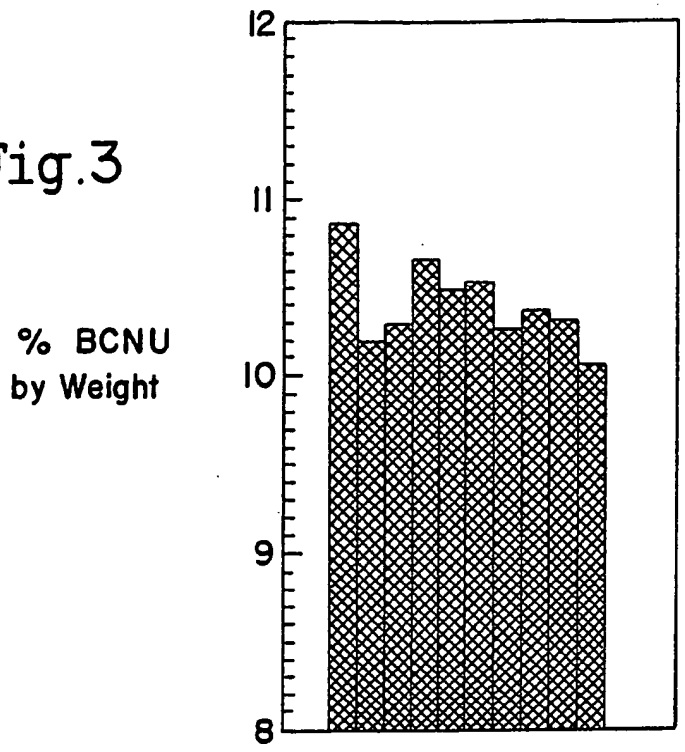


Fig.4
PRIOR ART

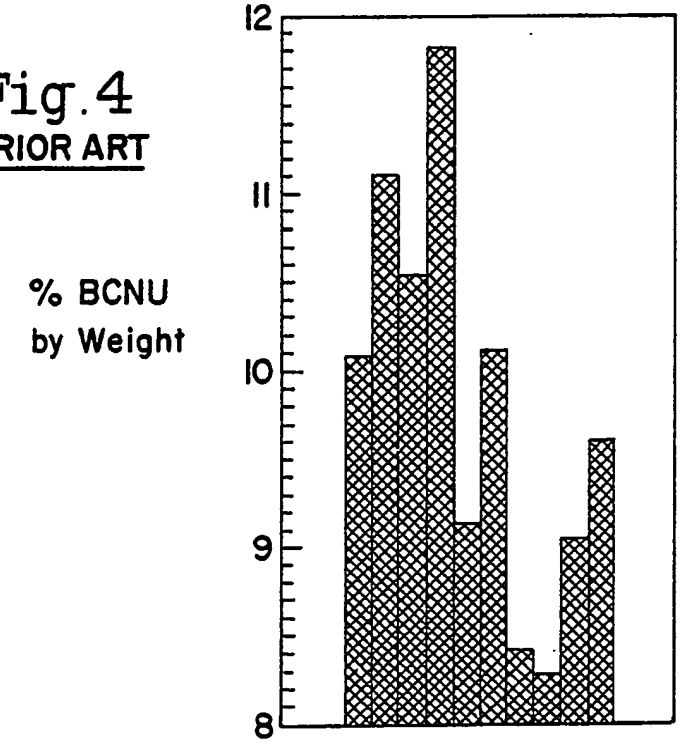


Fig.5

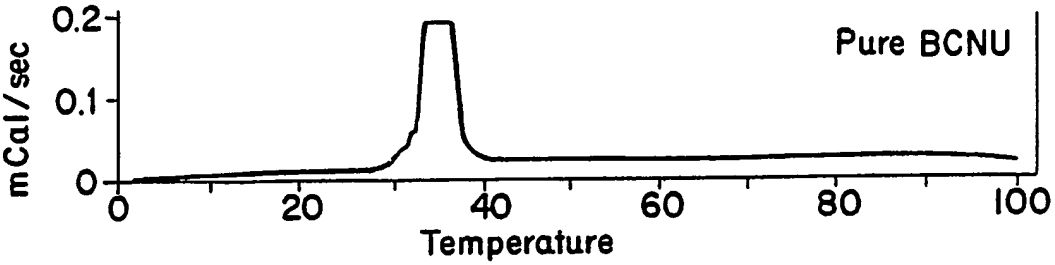


Fig.6

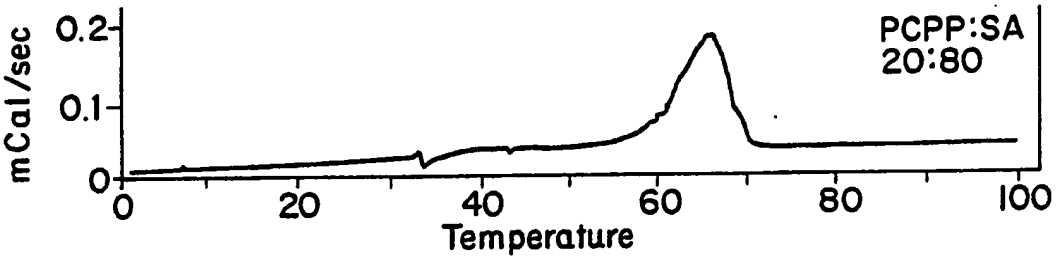


Fig.7
PRIOR ART

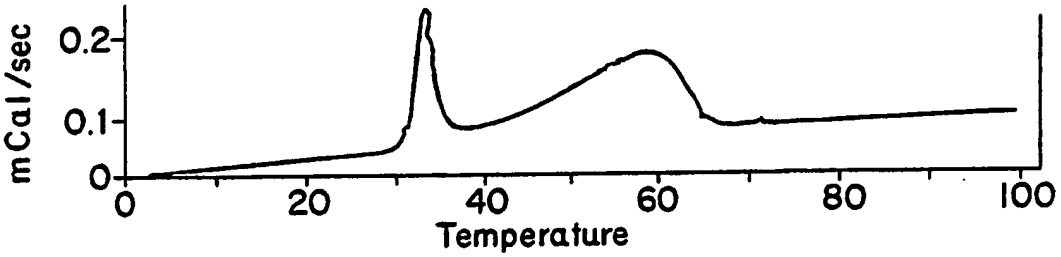
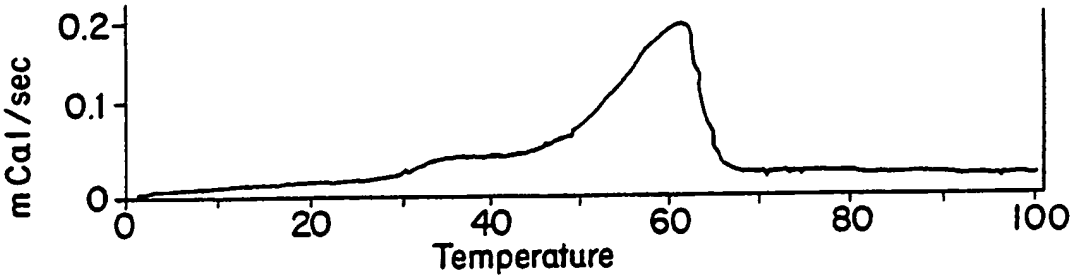


Fig.8



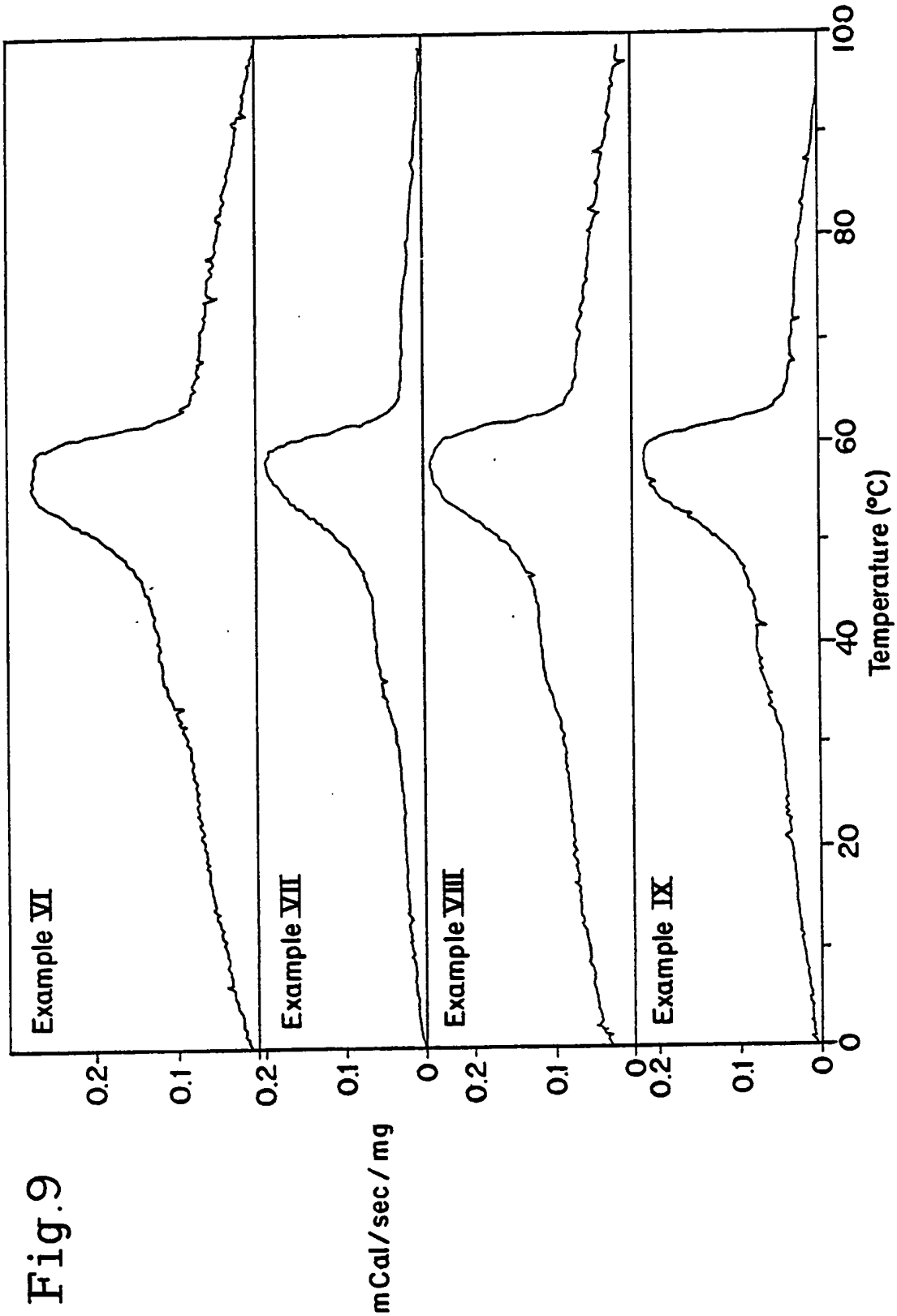
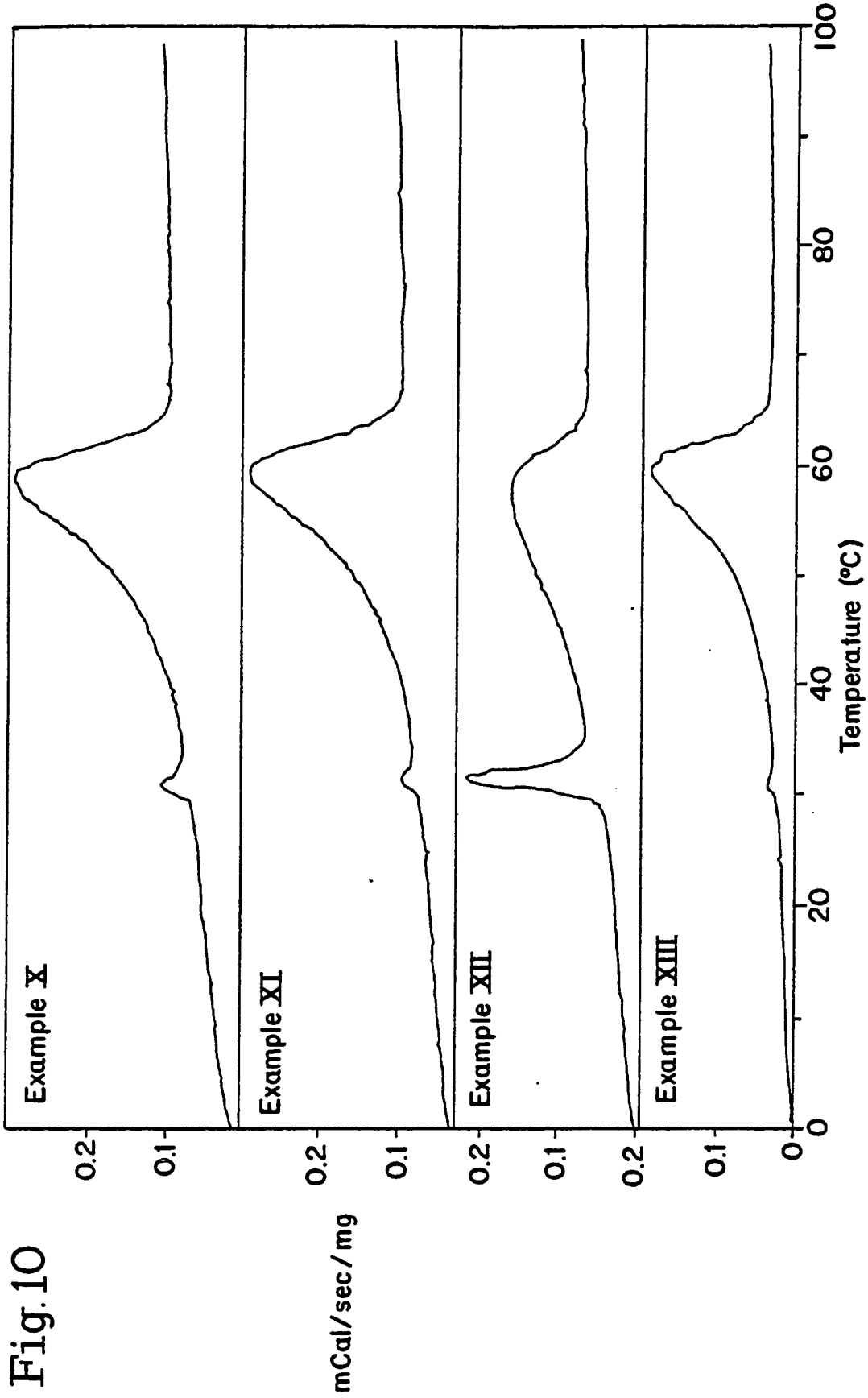

Example VI
Example VII
Example VIII
Example IX
0.2
0.1
0
0.2
0.1
0
0.2
0.1
0
0.2
0.1
0
mCal/sec/mg
0
20
40
60
80
100
Temperature (°C)

Fig.9


Example X
Example XI
Example XII
Example XIII
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0.1
0
mCal/sec/mg
0
20
40
60
80
100
Temperature (°C)

Fig. 10

Fig. 11

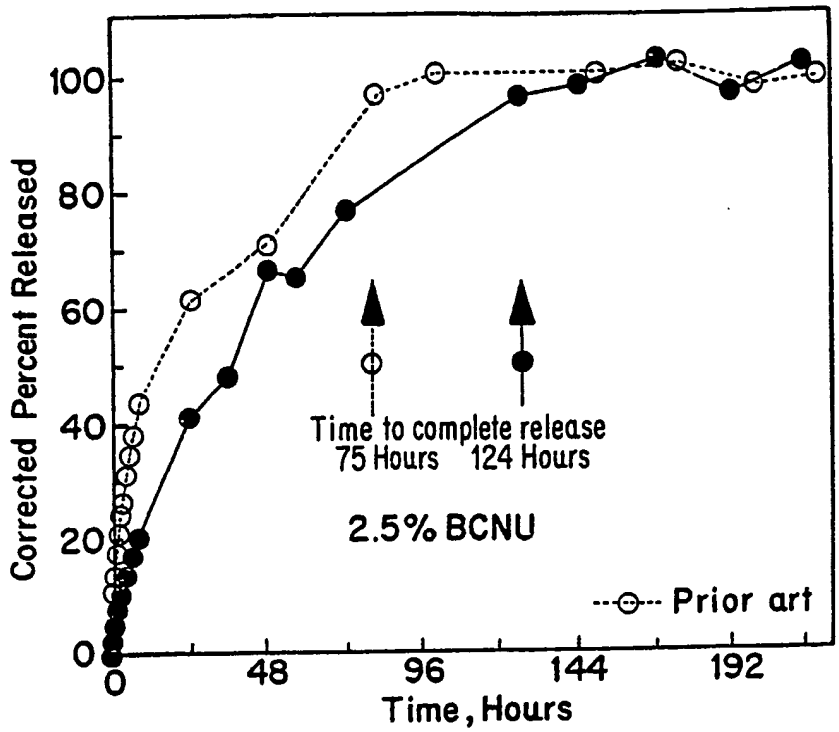
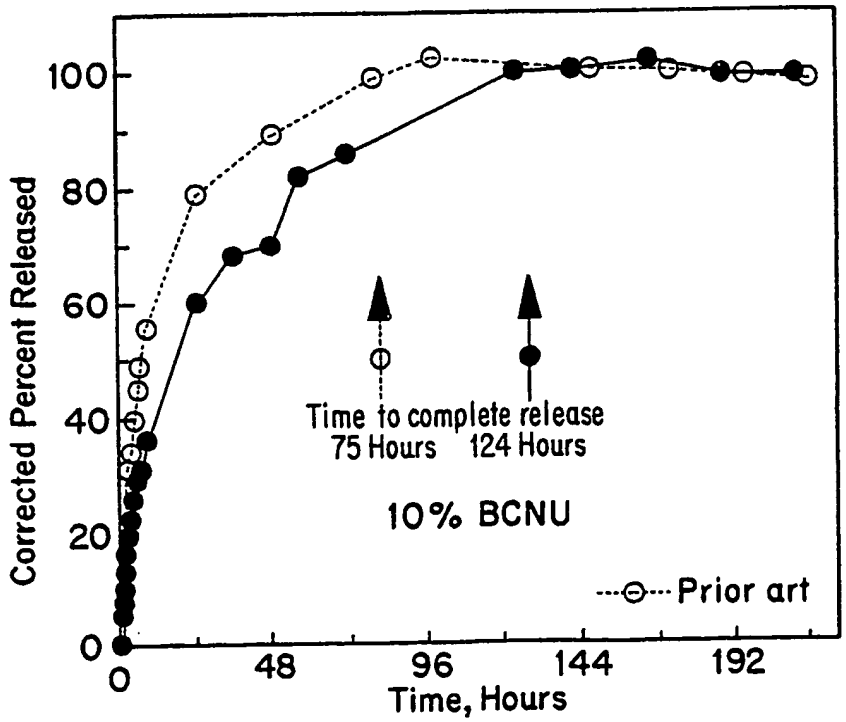

Corrected Percent Released
100
80
60
40
20
0
0
48
96
144
192
Time, Hours
Time to complete release
75 Hours 124 Hours
2.5% BCNU
Prior art

Fig. 12


Corrected Percent Released
100
80
60
40
20
0
0
48
96
144
192
Time, Hours
Time to complete release
75 Hours 124 Hours
10% BCNU
Prior art

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/04342

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

INT. CL(4): A61K 9/00, A61K 9/20, A61K 9/48
U.S. CL: 424/422, 424/425, 424/426

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	424/422 424/425, 424/426

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y,P	US, A, 4,767,627, PUBLISHED 30 AUGUST 1988, (CALDWELL ET AL): SEE ENTIRE DOCUMENT.	1-43
A	US, A, 4,357,312, PUBLISHED 02 NOVEMBER 1982, (HSIEH ET AL): SEE ENTIRE DOCUMENT.	
Y	EPO, A, 0,158,277, PUBLISHED 03 APRIL 1985, (SANDOW ET AL): SEE ENTIRE DOCUMENT.	1-43

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
06 FEBRUARY 1989	18APR 1989
International Searching Authority	**Signature of Authorized Officer**
ISA/US	Nancy A. B. Swisher NANCY A. B. SWISHER

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